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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/275,883	03/25/1999	WOLFGANG A. RENNER	1700.0020001	1349

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	22

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/275,883	RENNER ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-79,81-84,86-103,105-107 and 109-136* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *102* is/are allowed.

6)☒ Claim(s) *75-79,81-84,86-101,103,105-107 and 109-136* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on 2/27/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/275,883 is acceptable and a CPA has been established. An action on the CPA follows.

Applicant's amendment after final and the Declaration of Dr. Boorsma under 37 CFR 1.132, received 7/31/01, have been entered as Paper No. 18. Claims 80, 85, 104, and 108 were canceled and claims 126-136 were added as requested. Applicant's election with traverse of the species erythropoietin was acknowledged in Paper No. 11. The species "lymphokine, tumor necrosis factor, interferon, toxic protein, prodrug converting enzyme, and human beta interferon remain withdrawn from consideration. Claims 75-79, 81-84, 86-103, 105-107, and 109-136 are pending and under consideration in this office action.

Rejections Withdrawn

The Declaration of Dr. Boorsma under 37 CFR 1.132 was sufficient to overcome the portion of the enablement rejection relating to the scope of cells *in vitro* which the specification adequately teaches how to use.

The rejections of claims 75-101 and 103-125 under 35 USC 112, second paragraph are withdrawn in view of Applicant's amendments.

Claim Objections

Claim 79 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 79 is requires a polymerase of viral origin, but depends from claim 75 which requires that the polymerase must be alphaviral.

Claims 120-122 are iobjected to because they recite the ungrammatical phrase "at least DNA molecule". Addition of the word "one" between the words "least" and "DNA", in step (a) of claim 120 is suggested.

Claims 128, 132, and 136 are objected to because they recite "Easter". The appropriate term is "Eastern". These claims are also objected to because the 'm' in "morgan" should be capitalized.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-79, 81-84, 86-101, 103, 105-107, and 109-136 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record in Paper Nos. 11, 15, and 19.

The claimed invention encompasses the genus of DNA molecules comprising an open reading frame encoding a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase of alphaviral origin.

Applicant is referred to the interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64 Number 244, pp. 71427-71440 (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The central issue in this analysis is whether Applicant has disclosed a number of species which is representative of the claimed genus. Applicant discloses a single open reading frame encoding a Sindbis virus RNA-dependent RNA polymerase. This polymerase comprises a P726S nsP2 mutation in combination with a G153E nsP4 mutation. The P726S nsP2 and G153E nsP4

mutations are the structural features which are required to render the Sindbis virus polymerase both temperature sensitive and non-cytopathic. See paragraph bridging pages 21 and 22; page 22, lines 17 and 18; and page 23, lines 22-24. Temperature sensitivity and non-cytopathicity are the necessary common attributes which the polymerase must possess in order to qualify as a member of the claimed genus. However, the specification has failed to disclose what mutations are required to render any other RNA-dependent RNA polymerase both temperature sensitive and non-cytopathic, or what other mutations could confer this phenotype on the Sindbis virus polymerase. The state of the art of the prediction of protein function based on protein structure is not sufficiently advanced to predict *a priori* what mutations will confer temperature sensitivity or non-cytopathicity on a given RNA-dependent RNA polymerase, so it falls to the specification to provide this information. One of skill in the art appreciates that a wide variety of alphaviral RNA-dependent RNA polymerase is known in the art. In view of this recognized variety, and in view of the uncertainty associated with predicting which amino acid substitutions will confer temperature sensitivity and non-cytopathicity on a given polymerase, the disclosure of only a single species is considered insufficient to convey to one of skill in the art that applicant was in possession of the claimed genus at the time of the invention.

The courts have found that merely describing the functional characteristics of a protein encoded by a particular nucleic acid is insufficient to adequately describe the genus of nucleic acids encoding that protein. A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able

to define it so as to distinguish it from other materials, and to describe how to obtain it. See Oka, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g., non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. When an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The instant application does not provide a written description that would allow one of skill in the art to immediately envisage the specific structure for Sindbis virus non-cytopathic, temperature-sensitive RNA-dependent RNA polymerases, or for the broader genus of alphaviral non-cytopathic, temperature-sensitive RNA-dependent RNA polymerases. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed* (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed_" (See *Vas-Cath* at page 1116). As there is no disclosure of the polynucleotides, the skilled artisan

cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the broadly claimed polynucleotides at the time the application was filed. Thus it is concluded that the written description provision of 35 U.S.C 112, first paragraph, is not satisfied for the claimed polynucleotides. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C 112 is severable from its enablement provision (see page 1 1.1.5).

Applicant's arguments filed in Paper No. 18 on 7/31/01 were addressed in Paper No. 19. No further arguments accompanied the request for CPA.

Enablement

Claims 75-79, 81-84, 86-101, 103, 105-107, and 109-136 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA molecule encoding the Sindbis virus non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase with P726S nsP2 and G153E nsP4 mutations encoded by SEQ ID NO:1, does not

reasonably provide enablement for DNA molecules encoding any other alphaviral non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase, or for the use *in vivo* of any alphaviral particle, RNA or DNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons of record in Paper Nos. 11, 15 and 19.

The claims encompass nucleic acid molecules encoding a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase of alphaviral origin, methods of using the nucleic acids, alphaviral particles comprising the nucleic acids, and cells comprising the nucleic acids. The molecules encode an open reading frame which must undergo at least one RNA-dependent RNA polymerase-mediated replication event in order to be translatable. Claims 86, 93-101, 109, and 116-124 are methods of using the nucleic acids of the invention either *in vivo* or *in vitro*. The specification asserts no utility for using these nucleic acids *in vivo* other than gene therapy. The specification fails to enable the general practice of gene therapy for the reasons given in Paper No. 11. Briefly, the art of gene therapy is highly unpredictable, known delivery and expression systems are inadequate for therapeutic purposes, and the instant specification fails to complement the deficiencies of the prior art.

As discussed above, the specification discloses only a single example of a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase, yet the claims encompass the entire genus rather than just the single disclosed species. The prior art teaches several Sindbis virus polymerases which are temperature sensitive, and several other Sindbis virus polymerases which

are non-cytopathic. However, the specification fails to disclose any example, other than that encoded by SEQ ID NO:1, of a polymerase which is both temperature sensitive and non-cytopathic. While it is simple to construct nucleic acids which would comprise both types of mutations, the characteristics of these novel polypeptides would be highly unpredictable, as stated in the previous office actions. The reason for this is that it is not currently possible to accurately predict the effects of mutations on the function of proteins. For example, Rudinger (In peptide Hormones, J.A. Parsons Ed. University Park press, Baltimore, 6/1996) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study." See page 6, last paragraph. Furthermore, Schnizer et al (Arch Biochem Biophys. 1996 Feb 1;326(1):126-36) teach an example in which mutations of two separate amino acids of the yeast F1-ATPase beta subunit were combined and produced totally unpredictable results. Specifically, one mutation at position 203 and five different mutations at position 211 were found to inactivate and destabilize the F1-ATPase complex when expressed separately. However, when the position 203 mutation was combined with and any one of the position 211 mutations in the same construct, destabilization was suppressed and activity was restored to the ATPase complex. See abstract. While this result may allow certain conclusions to be drawn about structural and functional relationships within the ATPase, it could not have been predicted *a priori*. Similarly the effects of combining mutation in the Sindbis virus polymerases cannot be predicted a priori. One might argue that it would not be undue experimentation to express and

assay each construct individually and thereby determine empirically which ones encoded polymerases of the desired phenotype. However, as set forth in In re Fisher, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 11 11 2, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with degree of unpredictability of factors involved.

In this case, the art is not sufficiently advanced to allow the prediction of the effects of combining these mutations. Furthermore, Applicant has disclosed mutations only of a Sindbis virus polymerase, whereas the claims encompass RNA-dependent RNA polymerases from all alphaviruses. One of skill in the art could not predict which, if any, of these polymerases could be mutated to be appropriately temperature sensitive and non-cytopathic, or what mutations would be required for this.

In view of the unpredictability of the art of gene therapy, the unpredictability of polypeptide structure-function relationships, the failure of the specification to teach how to perform gene therapy, the failure of the specification to disclose more than one example of a Sindbis virus temperature sensitive, non-cytopathic RNA-dependent RNA polymerase, one of skill in the art could not make or use the invention commensurate in scope with the claims.

Applicant's arguments filed in Paper No. 18 on 7/31/01 were addressed in Paper No. 19. No further arguments accompanied the request for CPA.

Conclusion

Claim 102 is allowable.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JAMES KETTER
PRIMARY EXAMINER